

An Investigation of Dosimetric Consequences of the Anatomic Changes at First Fraction in VMAT of Prostate Cancer Cases using Deformable Planning CT and kVCBCT Image Registration

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ABSTRACT

Background: Kilovoltage Cone Beam Computed Tomography (kVCBCT) is used for patient setup, monitoring the delivered dose, and adapting the treatment to changes in the patient's condition. Radiation therapy has recently shifted from image guidance to dose guidance, resulting in accurately calculating the daily dose, calculated by re-simulating CT-based treatment planning, to increase the precision of the actual treatment dosage. The use of kVCBCT instead of re-simulated CT can simplify the patient pathway and reduce potential therapeutic errors by eliminating the need for additional simulation.

Objective: The present study aimed to assess the dosimetric effects of anatomical changes on prostate tumors using Deformation Image Registration (DIR) and kVCBCT.

Material and Methods: In this experimental study, eight patients with primary prostate cancer were treated with Volumetric Modulated Arc Therapy (VMAT), and kVCBCT images were obtained for each patient during the first treatment fraction. Both the planning CT (pCT) and kVCBCT images were imported into DIR software. The pCT was then deformed to the kVCBCT image and imported into a Treatment Planning System (TPS). A new contour was created on the deformed Computed Tomography (dCT) using Atlas-based Auto-segmentation (ABAS). Daily dCT plans were individually created based on the same planning principles using the new contours and also denoted dCTp1 through dCTp8. The outcomes of dose calculations were compared using Dose Volume Histograms (DVH), including mean Planning Target Volume (PTV) doses at the prescribed dose and dose volume limitations for the bladder and rectal wall.

Results: The mean doses to the PTV in the eight dCT-based plans were the same as those in the pCT-based plans. However, the mean doses to organs at risk in the dCT plans were different from those in the pCT plans. The mean doses to the bladder were on average 4% lower than those in the pCT plans, while the mean doses to the rectum were on average 8% higher than those in the pCT plans.

Conclusion: The use of VMAT based on kilovoltage kVCBCT and Deformation Image Registration (DIR) can lead to re-decreasing the dose to the bladder while increasing that to the rectum, with the same PTV dose coverage.

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Keywords

Cone-Beam Computed Tomography; Deformable Image Registration; Optical Flow; Radiotherapy; Dose Distribution; Prostatic Neoplasms

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Introduction

Volumetric Modulated Arc Therapy (VMAT) is considered an established treatment modality for prostate cancer cases [1] and is also used in the management of prostate cancer to maximize the tumor dose while minimizing radiation exposure to nearby organs with the assumption of static patient geometry. However, organ motion, weight anatomic, and setup changes can be noticed during the treatment course. The geometrical variations during the treatment course could lead to dosimetric variations, such as overdosage or underdosage to critical organs of risks and treatment the targets since conformality index is a function of patient geometry [2]. As a result, in-room: Kilovoltage Cone Beam Computed Tomography (kVCBCT) was developed to verify whether the intended dose is precisely delivered to the treatment target and critical Organ at Risk (OAR). Radiation therapists can detect any differences between this imaging set and the planning Computed Tomography (pCT) using kVCBCT before treatment, resulting in a decision whether the treatment plan is progressing as scheduled or needs replanning, or if the repositioned patient. In addition to kVCBCT, Deformable Image Registration (DIR) is introduced in clinical radiotherapy to evaluate the dosimetric consequences of anatomic prostate tumor variations by registering the pCT with the kVCBCT in a process called Adaptive Radiation Therapy (ART) [2]. “ART is defined as a close-loop, iterative process, in which the treatment plan is modified based on feedback measurements performed during treatment” [3]. Accordingly, DIR as a fundamental tool in the radiotherapy field evaluates geometrical deformations of treatment targets and critical organs with day-to-day Image-guided Radiation Therapy (IGRT) [4-5]. For instance, the DIR system is used in ART to compute the accumulated dose through re-planning on daily kVCBCT images, which are acquired

immediately before the treatment fraction. It is also used to translate the dose, propagate the contour, and compute the accumulated dose for intra-fraction radiotherapy using a Distance Vector Field (DVF) [6-8]. In radiotherapy, deformable registration can spare normal tissue and improve target dose coverage. However, image artifacts are associated with all imaging modalities, due to the difference between the mathematical assumptions and the experimental setup in the algorithm of image reconstruction. The Feldkamp algorithm, a reconstruction algorithm for kVCBCT, is adapted from the Filtered Back Projection (FBP) algorithm in the reconstruction of fan beam CT. In addition, this algorithm for kVCBCT shows that image quality is a function of the distance between the central and peripheral planes. A larger Field of View (FOV) results in a larger quantity of detected scatter radiation, significantly degrading image quality. The use of kVCBCT images for dose calculation led to inaccurate kVCBCT-based dose calculation due to the artifact effects, resulting in inaccurate HU values. The hardware-based corrections, such as anti-scatter X-ray grids on the detector, collimators, bowtie filters, and deformable image registration are adapted to minimize image artifacts [7].

In this study, an open-source DIR software was used in combination with pCT, daily kVCBCT images, and the Monaco Treatment Planning System (TPS) from Elekta Centers for Medicare & Medicaid Services (CMS) in Maryland Heights, MO, USA. The present study aimed to evaluate the effects of anatomic variations during prostate VMAT on the delivered dose to both the treatment target and critical organs at risk.

Material and Methods

This experimental study evaluates the dosimetric influence of anatomical changes in prostate cancer treated with VMAT using daily kVCBCT.

Image acquisition

Eight patients, who received VMAT treatment for prostate cancer in 2021, participated in the study, and each patient had one pCT and one daily in-room kVCBCT, using X-ray Volume Imaging (XVI) on the Versa-HD Elekta X-ray volume imaging system (Elekta, Crawley, UK). The kVCBCT images were acquired during the first fraction using the XVI in a standard pelvic acquisition mode. Table 1 presents the details of the data acquisition for pCT and kVCBCT.

Design of radiotherapy plan

The designs of radiotherapy plan for pCT and deformed Computed tomography (dCT) are summarized in Table 2.

Deformable Image Registration

During the first treatment fraction, the pCT

and the in-room kVCBCT were manually exported from the TPS. The original pCT included segmentations of the treatment targets and critical structures at risk. The data were then imported into an open-source deformable image registration software, which is called Deformable Image Registration and Adaptive Radiotherapy (DIRART) (<https://github.com/krishprince/dirart>). The voxel dimensions of the kVCBCT images and the pCT images were different; all image datasets were resampled using trilinear interpolation to achieve a uniform voxel dimension of $1 \times 1 \times 3 \text{ mm}^3$.

In the DIRART software, the optical flow algorithm was verified for the registration of different imaging modalities and also used for deformable pCT and kVCBCT image registration using two-step registration methods [5, 9]. The pCT and kVCBCT images were used as the moving and target images,

Table 1: Acquisition data of planning computed tomography (pCT) and kV Cone Beam Computed Tomography (kVCBCT) data for prostate cancer cases.

Parameters	Original computed tomography (CT) modality	Kilovoltage cone beam computed tomography modality
Company	Philips CT scanner	Versa- High Definition (HD) Elekta X-ray Volume Imaging (XVI) onboard volumetric imaging system (Elekta, Crawley, UK)
Matrix	512×512×168	410×410×84
Voxel size	0.1×0.1×0.3 cm ³	0.1×0.1×0.3 cm ³
Prime factors values	120 KeV and 213 mA over 470s	120 KeV and 64 mA over 40s

Table 2: Parameters of radiotherapy plan design used in this study.

Parameters	Description
Number of fields	One field for each patient and each field with 231, 250, 244, 253, 243, 255, 244, and 232 for patients 1, 2, 3, 4, 5, 6, 7, and 8 respectively.
The prescribed dose to the Planning Target Volume (PTV)	2.18 Gray (Gy)×34 fractions
The objectives	The 95% prescribed dose covers 100% of the treatment target volume. Rectum (<40% to receive ≥40 Gy), the total bladder (<40% to receive ≥40 Gy), and femoral heads (<40% to receive ≥30 Gy)).

respectively. The pCT image was then deformed to the kVCBCT image using the DIR system, involving a rigid registration, followed by a two-step deformable registration of the pCT to each kVCBCT while contouring the critical organs (Eq 1) [5]:

$$I = I_{\text{average}} + C \quad (1)$$

where I_{average} and C represent the averaged image intensity and a constant value of 800 for the rectum and bladder, and 1200 for subcutaneous fat and the target organ.

First, the rigid registration was performed, and then the deformable vector field was acquired. The acquired DVF was used to deform and propagate the scan to the kVCBCT. Figure 1 shows the process of deformable registration for a patient. All dCT and kVCBCT corresponding structures were saved in DI-

COM format and imported into the TPS. The original treatment plan was then copied over, and the dose of the critical organs was evaluated on the dCT.

DIR evaluation

The registration accuracy was evaluated using the 95% Hausdorff Distance (HD95) and Dice Similarity Coefficient (DSC) indices according to TG132 [10]. HD95 is used to measure the distances between two subsets of a metric space. The 95th percentile HD (HD95) is used instead of the 100th percentile HD (HD100) to eliminate the subsets of outliers. A lower HD95 value indicates a higher correspondence between the deformed and kVCBCT-based structures. Jassim et al. (2023) recommended that the HD95 value should be

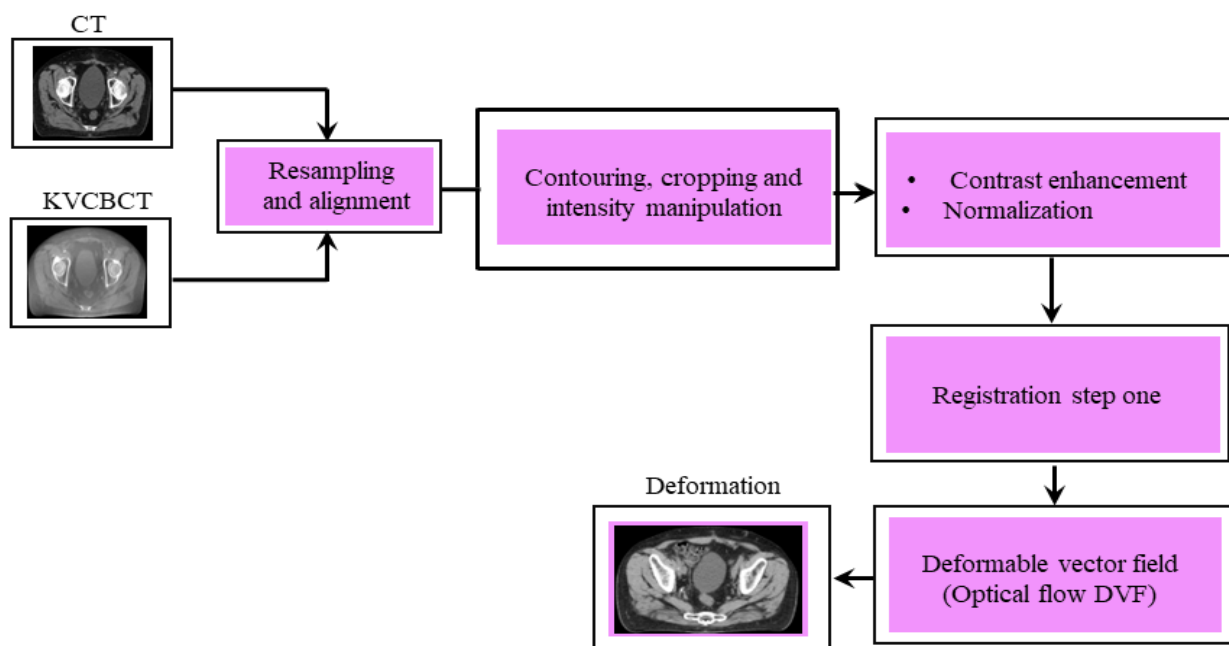


Figure 1: The overall workflow for the combined method: (1) importing the kVCBCT images and the pCT images into deformable image registration software, with different voxel dimensions; all image datasets were resampled using trilinear interpolation to achieve a uniform voxel $1 \times 1 \times 3 \text{ mm}^3$. Treatment targets and critical organs at risk were contoured once resampling images. The voxels of these structures were then updated using the CT number of bones. Finally, the whole pCT image was deformed by using the Displacement Vector Field (DVF) from the first step. (CT: Computed Tomography, KVCBCT: kV Cone Beam Computed Tomography, pCT: planning Computed Tomography)

within 0.3 cm for ART of the pelvis [8], which is calculated using the function defined in the Computation Environment for Radiotherapy Research (CERR) [11].

The DSC score is a measure of the overlap between two volumes (X, Y), i.e., 1 and 0 show the high and zero degrees overlapping [12]. The DSC score is ≥ 0.8 seems proper for adaptive radiotherapy of the pelvis [10], computed as follows (Eq 2):

$$DSC = \frac{2|X \cap Y|}{|X| + |Y|} \quad (2) [12].$$

Plan evaluation and statistical analysis

The prescription dose of the CT plan was 74 Gy delivered over 34 fractions, with the planning objective of distributing the dose over 95% of the PTV volume. The mean dose of the treatment target was evaluated for the bladder and rectum with the same evaluation for both the pCT and dCT plans. Statistical analysis was performed using the Excel Package software (Microsoft® Excel® 2016 MSO (Version 2305 Build 16.0.16501.20074) 64-bit), including descriptive and inferential analyses. Mean, percentage difference, and significant tests were calculated (*P* and *Z* values). Paired two-tailed t-tests were used to compare the pCT- and dCT-based planning at a statistical significance of *P*-value < 0.05 and a confidence level of 95%. Mean absolute error (MAE) was also computed to measure the absolute average value of the error between the predicted and reference values. In the current study, the predicted values were mean doses of the dCT-based plan, and the reference values were mean doses of the pCT-based plan. When the MAE is low, the predicted value is considered more accurate. The MAE is computed using a specific equation (3):

$$MAE = \frac{\sum_{i=1}^n \|CT_{pre}(x_i) - CT_{ref}(x_i)\|}{n} \quad (3)$$

where *n* is the total number of patients (x_i), CT_{pre} is the parameter calculated in dCT, and

CT_{ref} is the parameter calculated in the pCT image [11].

Results

Both HD95 and DSC values were computed for both rigid and deformable registration techniques. The rigid registration used pCT and kVCBCT images of the pelvis for the first fraction, while the deformable registration used dCT and kVCBCT images of the pelvis for the first fraction. The body, bladder, rectum, and prostate were contoured for both techniques. The average values of HD95 for the rigid and deformable registrations were 1.2 cm and 0.28 cm for the body, 1.3 cm and 0.27 cm for the bladder, 0.81 cm and 0.29 cm for the rectum, and 0.76 cm and 0.29 cm for the prostate. Figure 2 shows the average values of DSC for the rigid and deformable registrations. As depicted in Figure 2, the DSC values improved with DIR, with the average DSC values exceeding 0.8 for all critical organs.

Table 3 presents the volume measurements for the treatment target and OAR using both pCT and dCT plans. The extent of tumor shrinkage was not significant for these patients during the interval period between treatment planning and the first fraction of treatment, ranging of 0.05% to 0.064% with an average change of 0.04%. However, variable extents of critical organ variations were more observed in the dCT images relative to the pCT images, with the bladder experiencing a change range of 8.99% to 51.37% and an average change of 29.89%, and the rectum experiencing a change range of 4.50% to 69.01% and an average change of 26.85%. The critical value for the *Z*-value was 1.96. The volume measurements for the OAR and treatment target were reported in cubic millimeters (mm^3).

Figure 3 displays the DVH metrics results versus the dose distributions, which are computed on the PCT anatomy and kVCBCT images respectively. Figure 3 presents mean dose distribution is different between the

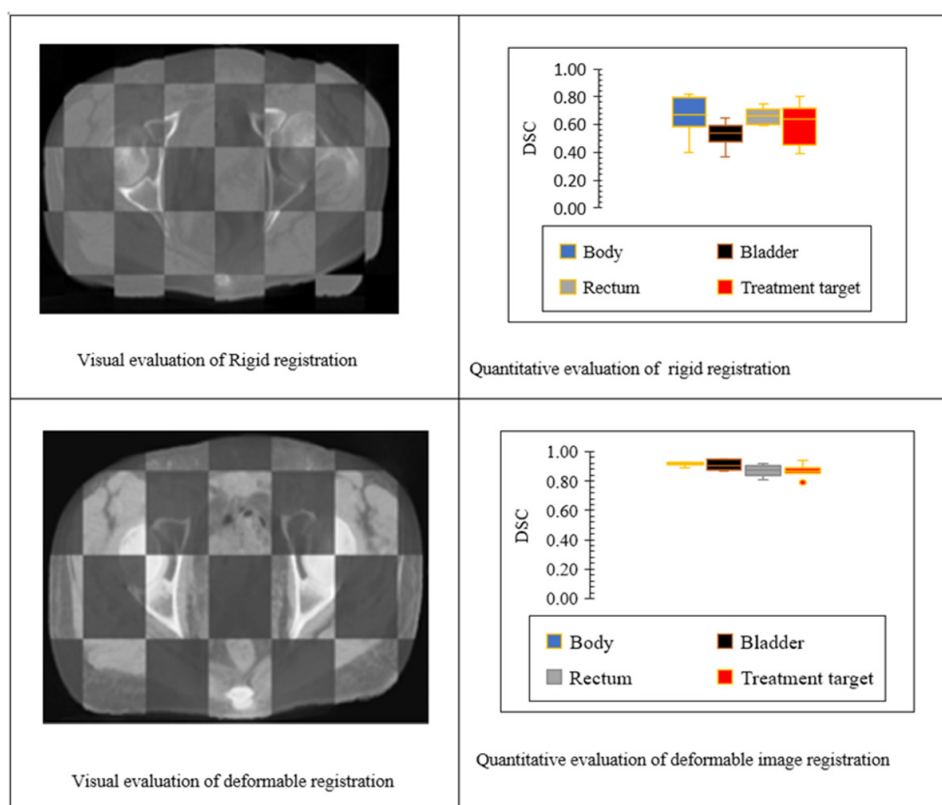


Figure 2: Evaluation check and comparison of DSC for rigid and deformable image registration. In the left column, DIR improved registration when compared with rigid registration, with DSC values of more than 0.8.

(DSC: Dice Similarity Coefficient, DIR: Deformable Image Registration)

Table 3: Volume for organs at risk and treatment target using the planning computed tomography and the deformed computed tomography plans. The critical value for Z-value was 1.96.

Patient number	Planning target volume		Bladder		Rectum	
	planning computed tomography	deformed computed tomography	planning computed tomography	deformed computed tomography	planning computed tomography	deformed computed tomography
Patient (1)	241.6334	240.082	252.976	176.068	237.9562	228.2225
Patient (2)	46.9876	47.196	139.4067	201.928	61.0914	252.976
Patient (3)	273.3765	273.584	63.4031	57.702	65.1275	139.4067
Patient (4)	414.7911	416.448	430.0289	209.112	48.1482	63.4031
Patient (5)	225.3342	225.226	70.1981	79.9	82.2659	430.0289
Patient (6)	241.6334	198.474	252.9716	195.042	40.1001	70.1981
Patient (7)	186.5197	151.186	139.4067	282.428	61.0914	252.9716
Patient (8)	412.9721	399.01	209.112	430.029	59.99	149.40
P-Value	0.77		0.69		0.049	
Z-Value	0.29		0.39		2.36	

pCT- and dCT-based planning for all structures. The percentage differences in mean dose were 0.04%, 16.46%, and 24.19% for the target, rectum, and bladder, respectively.

For the eight prostate cancer cases, the mean dose for the PTV and rectum had an average increase of 1% and 8%, respectively, while the bladder had an average decrease of 4% (P -value<0.05). Table 4 shows the dosimetric

changes of the treatment target and critical organs at risk for eight patients as a function of volume changes using the pCT and dCT images with a 1.96 for the critical value of the Z-value.

Discussion

The use of kVCBCT has improved radiotherapy treatments in the context of

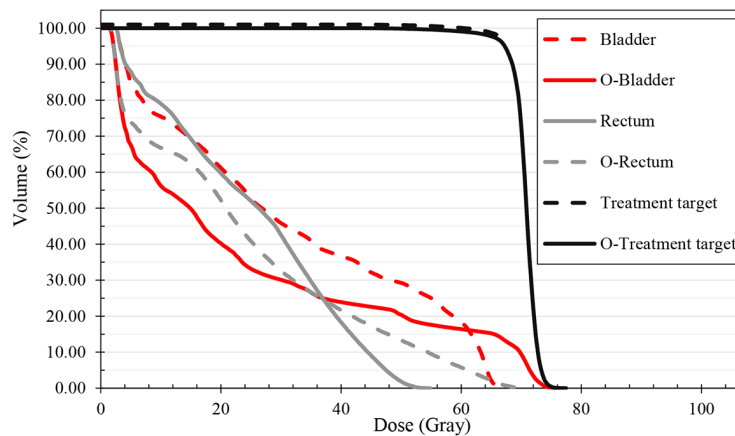


Figure 3: Comparison of the percentage difference between the mean doses of pCT and dCT images for the test datasets of eight patients at the first fraction.

(O-Bladder: Original Bladder, O-Rectum: Original Rectum, O-Treatment Target: Original Treatment Target, pCT: planning Computed Tomography, dCT: deformed Computed Tomography, PTV: Planning Target Volume)

Table 4: Metric differences of the absolute dose for the planning computed tomography and deformed computed tomography compared averaged over eight prostate cancer cases.

Patient number	Planning target volume (mean dose)		Bladder (maximum dose)		Target (mean dose)	
	planning CT	deformed CT	planning CT	deformed CT	planning CT	deformed CT
Patient (1)	69.83	67.24	76.85	75.35	23.855	31.93643
Patient (2)	70.83	70.19	74.45	74.55	34.131	33.9468
Patient (3)	70.45	70.50	73.85	75.65	31.3675	37.8966
Patient (4)	69.87	69.10	75.85	78.65	39.132	39.2355
Patient (5)	70.21	70.60	75.75	74.85	32.2486	31.9157
Patient (6)	69.83	68.50	76.85	41.0116	23.855	30.794
Patient (7)	70.56	70.00	74.45	67.15	34.131	43.6599
Patient (8)	70.45	69.50	73.85	65.85	31.3	29.1301
MAE	0.32		0.1875		1	
P-Value	0.05		0.20		0.18	
Z-Value	1.19		1.56		1.07	

Adaptive Radiotherapy (ART) and Image-Guided Radiotherapy (IGRT). Health professionals utilize kVCBCT to image the patient directly before treatment to assess changes in anatomy, such as patient weight loss and tumor shrinkage, and account for changes in the target position by adjusting the treatment. The re-simulated CT is used to account for the dosimetric effect of anatomical changes. However, using re-simulated CT is associated with several disadvantages, including increasing in complexity of the patient pathway, concomitant imaging dose to the patient, stressors on patients, waiting lists for patients, and health-care costs [5]. Given extensively validating dose recalculation using kVCBCT images, this study aimed to evaluate the dosimetric consequences of pelvic anatomic changes using DIR and kVCBCT.

The calculation of dose distribution in complex irradiation procedures, such as VMAT provides the most direct quality assurance, due to the prediction of the treatment effectiveness and the potential for normal tissue complications. Accurate daily dose calculations lead to monitoring and reporting doses, particularly with dose-guided ART, and computing the dosimetric effect of significant changes in patients' structures over the treatment course [4, 7, 13]. However, the kVCBCT images were used to calculate the dose and limitations, such as incorrect HU values and poor image quality reduced the strength of dose calculation [14-15]. Therefore, we utilized dCT images, which capture the features of the patient's structures during treatment to recalculate the dose distribution. The optical flow algorithm applied in the DIRART software, verified during the registration of different imaging modalities, can be used for deformable pCT and kVCBCT image registration using a two-step registration method. Hence, the dosimetric consequences of anatomical change were assessed using kVCBCT and optical flow-based deformable image registration in image reconstruction through the DIRART software

package developed using MATLAB.

The use of DIR improved image quality and accurately propagated the structures from pCT to dCT (Figure 2). The DIR procedure was reasonable for dose calculation from kVCBCT. However, this procedure has some disadvantages, as follows: the ROIs and new organ contours were required due to the poor quality of kVCBCT images, the methods are not suitable for online assessment of patient dose calculation and dose distribution changes, and the process takes a long time of approximately 30 minutes, leading to introducing uncertainty factors, such as patient position changes and organ volume variations, and making it suitable only for offline assessment of patient dose calculation and dose distribution changes. The improvement of the image quality of kVCBCT is recommended to reduce the procedure time of kVCBCT-based dose calculation.

In terms of volume changes in prostate cancer cases, six cases of the rectum and four cases of the bladder experienced a volume increase of critical OAR, and two cases of the rectum and four cases of bladder experienced a volume reduction of critical OAR throughout the treatment. As a result, these changes led to dosimetric differences between the pCT- and dCT-based plans (4).

The dosimetric impact of anatomic changes is evaluated using kVCBCT. The dosimetric effect of six-dimensional inter-fraction setup errors, including vertical, longitudinal, lateral, yaw, roll, and pitch errors, was reported using daily onboard kVCBCT in prostate cancer treated with intensity-modulated radiation therapy and VMAT [16]. However, setup changes, organ motion, weight loss, and structure deformation can occur during the treatment course, resulting in differing the actual dose to the target and OARs from the estimated values. In this study, the mean dose of the treatment target was similar between dCT and pCT plans, with a percentage difference of only 1%. However, for critical organs at risk, particularly the rectum and bladder,

significant mean dose changes were observed for these patients, (Figure 3). The dCT plan had a lower mean dose for the rectum compared to the pCT plan, with a percentage difference of 4%. On the other hand, the dCT plan had a higher mean dose for the bladder compared to the pCT plan, with a percentage difference of 8%. Furthermore, visual and quantitative confirmation of the dose differences in the treatment target and critical organs indicated that the bladder had a greater volumetric change compared to the treatment target and rectum (Table 3).

However, kVCBCT has a limited FOV, leading to covering the complete treated anatomy region required for dose calculation, the treated anatomy region was adequately covered in the pelvis (prostate cancer cases). Therefore, only one consecutive kVCBCT scan was acquired with the couch at a specific position. kVCBCT is weak compared to pCT, resulting in not using dose calculation and contouring of tissues on these images. However, both contours and CT numbers can be propagated from the pCT to the kVCBCT images by applying for non-linear registration. Hence, the DIR will influence tissue contour correspondence, affecting accumulated dose, dose distribution, and dose calculation [1, 5, 6]. After importing pCT and kVCBCT, dCT was created with propagating scan, and the features of dCT image are that dCT has the CT number of pCT and geometry of kVCBCT. After producing dCT, it is transferred to the TPS. The dCT-based plan was created in deformed CT by copying pCT-based plan.

Some papers denote that Genito-urinary (GU) toxicity was related to the high mean dose, and rectal toxicity was related to V70 and high doses beyond the threshold doses. This study demonstrated that while the bladder mean dose in the dCT plan was lower than those in pCT plan, the rectum mean dose was higher than those in the pCT plan with a statistical significance. For the bladder, adaptive re-planning could decrease the dose to the

rectum and other soft tissue an adaptive re-planning could decrease the dose to the bladder. The weight loss of patients will affect the bladder, rectum, and target volumes. Thus, the effect of body shape change can on the dose distribution needs more investigation [17].

Higher doses of radiotherapy increase the probability of tumor control and the risk of complications to organs at risk. Therefore, the daily fractional planning dose must be verified to improve the radiotherapy effect. The use of kVCBCT and DIR can enable precise computation of bladder, rectum, target, and normal tissue doses to enhance the fractioned planning dose. The decrease in optimization method time for re-contouring, dose calculation, and adaptive re-planning can cause DIR to become a valuable tool in the adaptive radiotherapy field.

Conclusion

The proposed framework is successfully used for dose guidance and provides the actual dose distribution of the day for VMAT-based delivery of radiation in prostate cancer cases. Therefore, DIR and kVCBCT are used as complementary methods to explore ART, which may improve the therapeutic ratio of this treatment.

Authors' Contribution

N. Banaae provided a patient data set and revised the manuscript. HA. Nedaie contributed to the ideation and provided the infrastructure required for the work. Gh. Graily provided practical work. HH. Jassim contributed with ideation, editing, revising, and submitting the final version of the manuscript. All authors approved the final version of the manuscript.

Ethical Approval

This work was approved by the ethical committee of the Faculty of Associated of Medical Science, Tehran University of Medical Science, Tehran, Iran with this code: IR.TUMS.IKHC.REC.1400.290.

Informed Consent

All the participants signed the informed consent.

Conflict of Interest

None

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